WHAT IS CLAIMED IS:

1. An isolated nucleic acid encoding a polypeptide comprising at least one of the biological activities of OPG wherein the nucleic acid is selected from the group consisting of:

a) the nucleic acids shown in Figures 2B-2C (SEQ ID NO:120), 9A-9B (SEQ ID NO:122), and 9C-9D (SEQ ID NO:124) or complementary strands thereof;

b) nucleic acids which hybridize under stringent conditions with the polypeptide-encoding regions as shown in Figures 2B-2C (SEQ ID NO:120), 9A-9B (SEQ ID NO:122) and 9C-9D (SEQ ID NO:124);

c) nucleic acids which hybridize under stringent conditions with nucleotides 148 through 337 inclusive as shown in Figure 1A; and

d) nucleic acid which are degenerate to the nucleic acids of (a), (b) and (c).

2. The nucleic acid of Claim 1 which is cDNA, genomic DNA, synthetic DNA or RNA.

3. A polypeptide encoded by the nucleic acid of Claim 1.

4. The nucleic acid of Claim 1 including one or more codons preferred for Escherichia coli expression.

5. The nucleic acid of Claim 1 having a detectable label attached thereto.

6. The nucleic acid of Claim 1 comprising the polypeptide-encoding region of Figure 2B-2C (SEQ ID

NO:120), Figure 9A-9B (SEQ ID NO:122) or Figure 9C-9D (SEQ ID NO:124).

7. The nucleic acid of Claim 6 having the sequence as shown in Figure 9C-D (SEQ ID NO:124) from nucleotides 158-1297.

8. An expression vector comprising the nucleic acid of Claim 1.

9. The expression vector of Claim 8 wherein the nucleic acid comprises the polypeptide - encoding region as shown in Figure 9C-9D (SEQ ID NO:124).

10. A host cell transformed or transfected with the expression vector of Claim 8.

11. The host cell of Claim 10 which is a eucaryotic cell.

12. The host cell of Claim 11 which is selected from the group consisting of CHO, COS, 293, 3T3, CV-1 and BHK cells.

13. The host cell of Claim 10 which is a procaryotic cell.

14. The host cell of Claim 13 which is <u>Escherichia</u> <u>coli</u>.

15. A transgenic mammal comprising the expression vector of Claim 8.

16. The transgenic mammal of Claim 15 which is a rodent.

17. The transgenic mammal of Claim 16 which is a mouse.

18. A process for the production of OPG comprising:

growing under suitable nutrient conditions host cells transformed or transfected with the nucleic acid of Claim 1; and

isolating the polypeptide products of the expression of the nucleic acids.

19. A purifed and isolated polypeptide comprising OPG.

20. The polypeptide of Claim 19 which is mammalian OPG.

21. The polypeptide of Claim 20 which is human OPG.

22. The polypeptide of Claim 19 which is substantially free of other human proteins.

23. The polypeptide of Claim 21 having the amino acid sequence as shown in Figure 2B-2C (SEQ ID NO:121), Figure 9A-9B (SEQ ID NO:123), or Figure 9C-9D (SEQ ID NO:125) or a derivative thereof.

24. The polypeptide of Claim 23 having the amino acid sequence as shown in Figure 9C-9D (SEQ ID NO:125) from residues 22-401 inclusive.

25. The polypeptide of Claim 23 having the amino acid sequence as shown in Figure 9C-9D (SEQ ID NO:125) from residues 32-401 inclusive.

26. The polypeptide of Claim 19 which is characterized by being a product of expression of an exogenous DNA sequence.

27. The polypeptide of Claim 26 wherein the DNA is cDNA, genomic DNA or synthetic DNA.

28. The polypeptide of Claim 19 which has been modified with a water-soluble polymer.

29. The polypeptide of Claim 28 wherein the water soluble polymer is polyethylene glycol.

30. A polypeptide comprising:

an amino acid sequence of at least about 164 amino acids comprising four cysteine-rich domains characteristic of the cysteine rich domains of tumor necrosis factor receptor extracellular regions; and

an activity of increasing bone density.

31. A polypeptide comprising the amino acid sequence as shown in Figure 2B-2C (SEQ ID NO:121), Figure 9A-9B (SEQ ID NO:123) or Figure 9C-9D (SEQ ID NO:125) having an amino terminus at residue 22, and wherein from 1 to 216 amino acids are deleted from the carboxy terminus.

32. The polypeptide of Claim 31 comprising the amino acid sequence from residues 22-185, 22-189, 22-194, or 22-201 inclusive.

33. The polypeptide of Claim 32 further comprising an Fc region of human IgG1 extending from the carboxy terminus.

34. A polypeptide comprising the amino acid sequence as shown in Figure 2B-2C (SEQ ID NO:121), Figure 9A-9B (SEQ ID NO:123) or Figure 9C-9D (SEQ ID NO:125) having an amino terminus at residue 22, wherein from 1 to 10 amino acids are deleted from the amino terminus and, optionally, from 1 to 216 amino acids are deleted from the carboxy terminus.

35. The polypeptide of Claim 34 comprising the amino acid sequence from residues 27-185, 27-189, 27-194, 27-401, or 32-401 inclusive.

36. The polypeptide of Claim 35 further comprising an Fc region of human IgG1 extending from the carboxy terminus.

37. A polypeptide selected from the group consisting of:

huOPG [22-201]-Fc
huOPG [22-401]-Fc
huOPG [22-180]-Fc
huOPG met [22-401]-Fc
huOPG Fc-met [22-401]
huOPG met [22-185]
huOPG met [22-189]
huOPG met [22-194]
huOPG met [27-185]
huOPG met [27-189]
huOPG met [27-194]
huOPG met [32-401]
huOPG met-lys[22-401]
huOPG met [22-401]
huOPG met [22-401]-Fc (P25A)
huOPG met [22-401] (P25A)
huOPG met [22-401] (P26A)
huOPG met [22-401] (P26D)

huOPG met [22-194] (P25A)
huOPG met [22-194] (P26A)
huOPG met met-(lys)$_3$ [22-401]
huOPG met met-arg-gly-ser-(his)$_6$ [22-401]

38. A nucleic acid encoding the polypeptide of Claim 37.

39. An antibody or fragment thereof which specifically binds to OPG.

40. The antibody of Claim 39 which is a monoclonal antibody.

41. A method for detecting the presence of OPG in a biological sample comprising:

incubating the sample with the antibody of Claim 39 under conditions that allow binding of the antibody to OPG; and

detecting the bound antibody.

42. A method to assess the ability of a candidate substance to bind to OPG comprising:

incubating OPG with the candidate substance under conditions that allow binding; and

measuring the bound substance.

43. A method of regulating the levels of OPG in an animal comprising modifying the animal with a nucleic acid encoding OPG.

44. The method of Claim 43 wherein the nucleic acid promotes an increase in the tissue level of OPG.

45. The method of Claim 44 wherein the animal is a human.

46. A pharmaceutical composition comprising a therapeutically effective amount of OPG in a pharmaceutically acceptable carrier, adjuvant, solubilizer, stabilizer and/or anti-oxidant.

47. The composition of Claim 46 wherein the OPG is human OPG.

48. The composition of Claim 47 wherein the OPG has the amino acid sequence as shown in Figure 9B.

49. A method of treating a bone disorder comprising administering a therapeutically effective amount of the polypeptide of Claim 19.

50. The method of Claim 49 wherein the polypeptide is human OPG.

51. The method of Claim 49 wherein the bone disorder is excessive bone loss.

52. The method of Claim 51 wherein the bone disorder is selected from the group consisting of osteoporosis, Paget's disease of bone, hypercalcemia, hyperparathyroidism, steroid-induced osteopenia, bone loss due to rheumatoid arthritis, bone loss due to osteomyelitis, osteolytic metastasis, and periodontal bone loss.

53. The method of Claim 49 further comprising administering a therapeutically effective amount of a substances selected from the group consisting of bone morphogenic proteins BMP-1 through

BMP-12, TGF-β family members, IL-1 inhibitors, TNFα inhibitors, parathyroid hormone and analogs thereof, parathyroid hormone related protein and analogs thereof, E series prostaglandins, bisphosphonates, and bone-enhancing minerals.

54. An osteoprotegerin multimer consisting of osteoprotegerin monomers.

55. The multimer of Claim 54 which is a dimer.

56. The multimer of Claim 54 formed by interchain disulfide bonds.

57. The multimer of Claim 54 formed by association Fc regions derived from human IgG1.

58. The multimer of Claim 54 which is essentially free of osteoprotegerin monomers and inactive multimers.

59. The multimer of Claim 54 wherein the monomers comprise the amino acid sequence as shown in Figure 9C-9D (SEQ ID NO:125) from residues 22-401, or a derivative thereof.

60. The multimer of Claim 54 wherein the monomers comprise the amino acid sequence as shown in Figure 9C-9D (SEQ ID NO:125) from residues 22-194.

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